Altered monoaminergic systems and depressive-like behavior in congenic prion protein nnock-out mice

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LETTER

Altered Monoaminergic Systems and Depressive-like Behavior in Congenic Prion Protein Knock-out Mice

Beckman *et al.* (1) reported altered monoaminergic systems and depressive-like behaviors in a line of mice lacking the cellular prion protein PrP^{C} (congenic B10.129-*Prnp*$^{Edbg/Edbg}$ mice). These mice were derived from gene-targeted 129/Ola embryonic stem cells and were subsequently crossed to C57BL/10SnJ mice. Consequently, the genomic region of B10.129-*Prnp*$^{Edbg/Edbg}$ mice flanking the targeted *Prnp* locus contains a stretch of up to 47.4 Mb isogenic to 129/Ola (2). In this region, any genes polymorphic between the 129/Ola and C57BL/10SnJ strains will display 129/Ola allelotypes (2). This genetic anomaly represents a systematic confounder when congenic knock-out mice are compared with wild-type mice of the back-crossing strain, even when using littermates from heterozygous breedings (2). This phenomenon, intrinsic to all congenic knock-out mice, is known as the flanking gene problem.

The genetic background has a strong influence on depression-related behavior in mice (3). Numerous studies have identified multiple genes and quantitative trait loci controlling monoaminergic systems and depressive-like behaviors. Crucially, these include *Sirpa*, which is linked to *Prnp* (genetic distance: approximately 2 centimorgans), is polymorphic between C57BL and 129 strains, and is a known genetic confounder of studies with *Prnp*$^{-/-}$ mice (4, 5).

For the above reasons, the published data (1) do not allow conclusive determination of whether the phenotypes observed are caused by the ablation of *Prnp*, by the *Sirpa* polymorphism discussed above, or by other sequence polymorphisms in the genomic region flanking *Prnp*. The conclusion that PrP^{C} participates in the modulation of monoaminergic systems and depressive-like behavior is therefore unwarranted.

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